Medical and Pediatric Oncology 26:325–328 (1996)

Compensatory Hypertrophy and Progressive Renal Damage in Children Nephrectomized for Wilms' Tumor

M.T. Di Tullio, MD, F. Casale, MD, P. Indolfi, MD, C. Polito, MD, M. Giuliano, MD, A. Martini, MD, E. Cimmaruta, MD, C. Morgera, MD, F. Cioce, MD, and N. Greco, MD

Clinical, biochemical, and sonographic evaluation of the remaining kidney function and size was performed in 34 patients, 12 males and 22 females, ages 2.1–19.6 years, nephrectomized (NP) for Wilms' tumor (WT) at least 2 years before (mean 8.6). All patients had normal blood pressure and serum bicarbonates. Two of them had microhematuria, four proteinuria 4 mg/m2/hr, and 11 microalbuminuria (MA) >20 mg/24 hr. Only one patient had reduced creatinine clearance and maximum bipolar length (MBL) as well as kidney volume (KV) <100% of expected. In the other patients, average MBL was 128 ± 14% and KV was 213 ± 11% ($P = 0.0001$). MBL, but not KV, was inversely correlated ($P = 0.04$) to age at NP. KV, but not MBL, was directly correlated ($P = 0.009$) to MA. Average MA was 48 ± 94 mg/24 hr and was correlated to the time from NP ($P = 0.026$). The remaining kidney increases in volume much more than in length. The increase in KV is related to the degree of MA, whereas the increase in MBL is higher in subjects younger at NP. The high prevalence of significant MA, which is in turn related to the time from NP and to the KV, raises some concerns about the long-term renal prognosis of children NP for WT.

Key words: unilateral nephrectomy, Wilms' tumor, kidney size, microalbuminuria, compensatory hypertrophy

INTRODUCTION

In children nephrectomized (NP) for Wilms' tumor (WT), the function of the remaining kidney is uncertain over the long term. This is because of the risk of glomerulosclerosis [1,2] and interstitial renal injury [3,4] that may lead to chronic renal failure. Glomerulosclerosis and proteinuria can also develop in those patients with congenital unilateral agenesis [2], likely because of the hyperfiltration secondary to the excessive work burden for the solitary kidney. In children NP for WT, the effects of radiotherapy and cytotoxic drugs could increase the risk of renal injury.

The availability of normal sonographic standards for kidney length and volume in children [5] facilitates the study of hypertrophy in the remaining kidney. Microalbuminuria (MA) reflects a slightly elevated urinary albumin excretion. It indicates an abnormal passage of plasma albumin into urine through the glomerular filter and likely depends on hyperfiltration through the glomerular capillary wall. Its prognostic significance has been well established in insulin-dependent diabetics in whom MA predicts progressive glomerular damage [6].

There are few sonographically assessed studies of kidney size and MA in children NP for WT. In this report, we describe the results of such an investigation.

MATERIALS AND METHODS

From the beginning of January to the end of February 1994, we studied 34 unselected patients, 12 males and 22 females, ages 2.1–19.6 (mean 12.1) years, NP for WT at least 2 years before (mean 8.6, range 2.7–15.8). All patients were off therapy. Preoperative radiology revealed a normal contralateral kidney in each case. They were treated following the Italian Research Council Nephroblastoma Study schedule [7]. After surgery, actinomycin D (15 mcg/Kg during 5 days on wks 1 and 6) and vincristin (1.5 mg/sq m per wk × 8, then biweekly × 8) were administered to patients having stages I–II WT with favorable histology. In patients with favorable or

From the Departments of Pediatrics (M.T.D.T., F.Ca., P.I., C.P., M.G., A.M., E.C., C.M.) and Radiological Science (F.Ci., N.G.), 2nd University of Naples, Naples, Italy.

Received November 22, 1994; accepted March 10, 1995.

Address reprint requests to M.T. Di Tullio, M.D., Clinica Pediatrica, via S. Andrea delle Dame, 4, 80138 Naples, Italy.

Part of this work was accepted for presentation at the XXVIth Meeting of the International Society of Pediatric Oncology, Paris, September 1994.

unfavorable histology, stage III WT or with unfavorable histology stages I–II, the treatment included adriamycin (50 mg/sq m) + vincristin given monthly, alternated with actinomycin D + vincristin by the 10th up to the 54th weeks. Preoperative actinomycin D + vincristin were administered to patients with stage IV or with unoperable WT. Radiotherapy (15–35 gy to tumor bed and/or abdomen) was given in stages II–III WT. Twenty-three patients received (R) and 11 received no radiotherapy (NR). Each patient who underwent radiotherapy had a shield to protect the contralateral kidney during treatment when receiving more than 12 gy.

The clinical-biochemical workup included: weight and height, blood pressure, urine analysis, serum bicarbonates, creatinine clearance (CCr) [8] and MA on 24-hour urine collection. MA was assayed by immunoturbidimetry. Values of CCr above 80 ml/min/1.73 sq m and of MA below 20 mg/24 hr were considered normal.

The ultrasound examinations were performed with a 3.75 MHz electronic convex scanner equipped with a freeze frame, calibration setting, and a water display (Toshiba SAL 250 SSA). The kidney size was always assessed by the same operator, using the method of Dinkel et al. [5], i.e., measurement of the maximum bipolar length (MBL) and the kidney volume (KV). The findings were plotted on the standards charts for normal children by Dinkel et al. [5]. For statistical analysis, MBL was *expressed* as percent of the mean value expected for the stature and KV as percent of the mean value expected for the weight of the subject [5]. During the study period, MBL and KV were also assessed by the same operator in nine children, ages 1.1–12 years (mean 5.1) with congenital unilateral agenesis (CUA). All subjects under study had a height within ±2SD of normal [9].

The differences between mean values were assessed by the t-paired and the Kruskall-Wallis test. The relation between series of values was studied by the Spearman test. Values of $P < 0.05$ were considered significant.

RESULTS

Table I reports the main clinical data of each patient. All patients had serum bicarbonates above 19 mmol/L and blood pressure within the normal range for age [10]. Two patients had microscopic glomerular type haematuria seen on phase-contrast microscopy, four had proteinuria >4 mg/m2/hr (range 10–32), and 11 MA above 20 mg/24 hr.

Only one out of the 34 patients (No. 30, Table I) had CCr below the normal (43 ml/min/1.73 sq m), serum creatinine of 1.6 mg/dL, MBL as well as KV below the 100% expected (respectively, 92% and 82%) and proteinuria of 32 mg/m2/hr. This was a 9.4-year-old girl NP at age 4.6 years for WT stage III HF who had started chemotherapy + radiotherapy as reported [7]. During therapy, she developed pulmonary methastases, for which chest radiotherapy and potentially nephrotoxic drugs (cisplatinum, ifosfamide) were administered. Because of the renal insufficiency and the relative renal hypoplasia, her data were not included in the statistical analysis of compensatory hypertrophy.

In WT patients, the average MBL was 128 ± 14% (range 112–173) and KV was 213 ± 11% (range 134–497), and the difference between MBL and KV values was significant ($t = 5.23$; $P = 0.0001$).

In CUA subjects, the average MBL was 134 ± 10% (range 113–154) and KV was 211 ± 29 (range 177–266). The difference between MBL and KV was significant ($t = 8.4$; $P = 0.0001$). No significant difference was found in KV and in MBL between WT and CUA subjects.

In WT patients, MBL—but not KV—was inversely correlated ($rs = -0.36$; $P = 0.04$) to age at NP. KV—but not MBL—was directly related ($rs = 0.47$; $P = 0.009$) to MA values. Mean MA was 48 ± 94 mg/24 hr and was related to the time from NP ($rs = 0.39$; $P = 0.026$).

No significant difference between R and NR patients was found in MBL (R = 127 ± 15%; NR = 128 ± 4%), KV (R = 234 ± 124%; NR = 189 ± 134%) and MA (R = 44.8 ± 83 mg/24 hr; NR = 54.7 ± 117).

DISCUSSION

The main findings of our study are the occurrence of renal insufficiency in one of the patients, the presence of elevated MA in about one-third of them, and the greater rise in volume than in length of the remaining kidney. The occurrence of reduced CCr, MBL, and KV and of nonnephrotic proteinuria in one of our patients, after a relatively short follow-up (4.8 years), highlights the risk for renal sclerosis and insufficiency in children NP for WT and treated with nephrotoxic drugs.

Wikstad et al. [11] found high MA values, which increased with a longer follow-up time, in 47% of adults born with CUA or NP in childhood because of hydronephrosis. Their follow-up period was very much longer than ours. The elevated MA in our series suggests that the glomerular capillary wall becomes more permeable to albumin following the compensatory renal growth, which starts in childhood after NP for WT. This raises a warning about the long-term prognosis of renal function in children NP for WT, all the more that also in our series MA increases with time from NP.

No significant difference in any of the parameters was found in our study between R and NR patients. The limited sample size and/or the protective effect of the shield in the R patients may explain this finding.

In another study [12], Wikstad et al. found that urographically assessed kidney size was significantly larger

TABLE I. Main Clinical Data of 34 Patients Nephrectomized for Wilms' Tumor

No.	Age at NP (yr)	Time since NP[a] (yr)	Irradiation dose (rads)	Nephrotoxic agents	CCr[b] (ml/min/173 sqm)	MA[c] (mg/24 hr)	MBI[d] (% of normal)	KV[e] (% of normal)
1	9.5	4.2	2,500	NO	103	7.7	128	139
2	3.8	5.1	2,500	NO	105	3.6	125	134
3	0.7	13.9	—	NO	76	5	114	204
4	4.9	9.6	—	NO	86	9.4	103	169
5	7.3	12.3	2,500	NO	97	148	128	297
6	3.9	5.9	2,500	NO	91	66	126	300
7	6.7	7.6	2,500	NO	96	3.9	118	155
8	2.9	8.7	—	NO	123	2.7	149	210
9	3.5	6.8	2,500	NO	116	3.3	128	159
10	0.9	8	—	NO	110	4	128	151
11	1.7	9.1	2,000	NO	118	2.7	126	169
12	0.6	9.8	—	NO	129	3.9	133	178
13	2.1	4.8	—	NO	101	208	130	188
14	4.9	12.4	2,500	NO	82	384	145	196
15	0.2	2.7	—	NO	106	0.7	137	173
16	0.4	4.2	—	NO	93	5.1	128	277
17	3.4	9.6	—	NO	118	4.9	130	197
18	1.1	11	2,000	NO	265	17.1	122	216
19	2.6	11.7	2,550	NO	116	49	122	232
20	2.6	7.4	2,100	NO	146	27	140	495
21	2.1	15.8	3,000	NO	104	18	120	212
22	2.2	7.5	2,500	NO	272	4.8	131	247
23	2.7	9	2,550	NO	93	62	173	179
24	1.3	10	1,500	NO	146	91	155	497
25	5.3	4.1	2,100	NO	112	6.5	136	423
26	2.1	12.8	2,100	NO	107	11.3	131	485
27	7.7	10.9	2,500	NO	88	5.9	114	156
28	0.6	9.6	—	NO	99	0.7	132	159
29	3.1	5.6	2,500	NO	90	48	118	133
30	4.6	5.2	2,550	Cis-PI, IFO[f]	43	42	92	82
31	2.2	14.4	2,800	NO	91	20	127	152
32	10.9	4	2,000	NO	95	3.4	116	168
33	5.8	7.1	2,500	NO	102	9.5	112	177
34	2.5	11.5	—	NO	105	357	132	177

[a]Nephrectomy.
[b]Creatinine clearance.
[c]Microalbuminuria.
[d]Maximum bipolar length.
[e]Kidney volume.
[f]Cisplatin (total dose = 180 mg/mq), ifosfamide (total dose = 18 gr/mq).

in 15 patients NP in childhood for hydronephrosis than in 22 NP in childhood for WT. In contrast, we were unable to demonstrate any difference in sonographically assessed KV and MBL between the patients NP for WT and the subjects born with CUA. The differences in methods, duration of follow-up, and kind of radiotherapy may help to explain these differences.

In our WT patients, the increase in KV was significantly higher than the increase in MBL. We also observed a significantly higher increase in KV than MBL in the group of children with CUA. Therefore, it seems that the greater increase in KV than in MBL is the usual way in which a unique (because of CUA or after NP) kidney hypertrophies. However, in children Nx for WT, this difference does not merely reflect an anatomical peculiarity depending on the available space for the growth of the remaining kidney. Indeed, KV and MBL correlate differently with clinical and prognostic data: the increase in KV is related to the degree of MA, whereas the increase in MBL is higher in the subjects who were younger at the moment of NP. An answer to this problem requires analysis of larger series of patients.

The inverse relationship between MBL and age at NP found in our patients agrees with that demonstrated in rats [13]: the younger the subject, the greater the compensatory hypertrophy of the remaining kidney. However, KV (but not MBL) is related to MA and therefore—roughly—with the risk that the work burden for the remaining kidney could lead to glomerulosclerosis and to renal insufficiency.

We conclude that the high prevalence of MA, which is in turn related to the time from nephrectomy and to KV, raises concerns about the long-term renal prognosis of children Nx for WT. The finding of renal insufficiency and of relative kidney hypoplasia in one patient who received nephrotoxic drugs is an additional warning about these medications in WT patients.

ACKNOWLEDGMENTS

The authors sincerely thank Dr. Giulio J. D'Angio for his critical review and helpful suggestions.

REFERENCES

1. Welch TR, McAdams AJ: Focal glomerulosclerosis as a late sequelae of Wilms' tumour. J Pediatr 108:105–109, 1986.
2. Gutierrez-Millet V, Nieto J, Praga M, Usera G, Martinez MA, Morales JM: Focal glomerulosclerosis and proteinuria in patients with solitary kidney. Arch Intern Med 146:705–709, 1986.
3. Mitus A, Tefft M, Fellers FX: Long-term follow-up of renal function of 108 children who underwent nephrectomy for malignant disease. Pediatrics 44:912–921, 1969.
4. Keane WF, Crosson JT, Staley NA, Anderson WR, Shapiro FL: Radiation induced renal disease. Am J Med 60:127–137, 1976.
5. Dinkel E, Ertel M, Dittrich M, Peters H, Berres M, Schulte-Wissermann H: Kidney size in childhood: Sonographical growth charts for kidney length and volume. Pediatr Radiol 15:38–43, 1985.
6. Mathiesen ER: Microalbuminuria in insulin-dependent diabetes: Strategies to prevent diabetic nephropathy. Nephron 65:511–521, 1993.
7. Fossati-Bellani F, Lombardi F, Pilotti S, Paolucci G, Di Tullio MT, Madon E, Tamaro P, Calnelli G, Ceci A, Del Vecchio M, De Palo G: The Italian Research Council Nephroblastoma Study: Wilms' tumor: Results of a prospective cooperative study. Med Pediatr Oncol 15, S147, 1989.
8. Schwartz GJ, Brion LP, Spitzer A: The use of plasma cretinine concentration for estimate glomerular filtration rate in infants, children and adolescents. Pediatr Clin North Am 34:571–590, 1987.
9. Tanner JM, Whitehouse RH: Clinical longitudinal standards for height, weight, height velocity, weight velocity, and stage of puberty. Arch Dis Child 51:170–179, 1976.
10. Task Force on Blood Pressure Control in Children: Report of the second task force in blood pressure control in children 1987. Pediatrics 79:1–25, 1987.
11. Wikstad I, Celsi G, Larsson L, Hering P, Aperia A: Kidney function in adults born with unilateral renal agenesis or nephrectomized in childhood. Pediatr Nephrol 2:177–182, 1988.
12. Wikstad I, Pettersson A, Elinder G, Sökücü S, Aperia A: A comparative study of size and function of the remnant kidney in patients nephrectomized in childhood for Wilms' tumor and hydronephrosis. Acta Paediatr Scand 75:408–414, 1986.
13. Celsi G, Jakobsson B, Aperia A: Influence of age on compensatory renal growth in rats. Pediatr Res 20:347–350, 1986.